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13. SUPPLEMENTARY NOTES

14. ABSTRACT
The current study is to use a targeted, LC-MS-based metabololite profiling platform to measure and compare metabolic profiles of prediagnostic blood samples collected from men subsequently diagnosed with prostate cancer (PCa) and sample of men who remained cancer-free in a prospective cohort of the Physicians' Health Study (PHS). And test whether the metabolomics profiling are related to 1) metastatic PCa at diagnosis as compared with normal controls; and 2) among PCa patients, related developing fatal outcome as compared with long-term survivors. We will also assess whether these associations are independent of the known metabolic risk factors (overweight/obese, insulin marker C-peptide, insulin-like growth factor I (IGF-I), IGF binding protein 3, (IGFBP-3), and adiponectin) as well as the clinical characteristics defined as the D'Amico risk. In the original protocol, we plan to measure samples of PCa cases from both HPFS and PHS. During the first year, we were working on informative case and control selection and during this period of time, the HPFS team has received separate grant for metabolomics measurement. We, therefore, amended our study population to focus only on the PHS samples but stick to our original planned 400 study participants. Based on the available samples, we utilized matched case control design to select the blood samples to be measured. The selected blood samples are currently being pooled in the blood lab and due to a big queue of work load at the blood lab, we are waiting for blood sample aliquating and boxing.

15. SUBJECT TERMS
Prostate cancer survivorship, metabolite profiling, metabolic biomarkers

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1. Introduction

A major challenge in prostate cancer (PCa) research is to distinguish aggressive from indolent disease. Although the clinical stage and Gleason grade-based risk stratification is helpful, it cannot always reliably distinguish patients who will die from PCa from those who do not. Our prospective studies of adiposity, physical activity, and several individual biomarkers in two large Harvard cohorts demonstrate that markers of energy metabolism such as insulin, adipokines, and *de novel* fatty acid synthesis may play important roles in risk of lethal PCa. Recent development of a metabolite profiling platform by Dr. Clish's laboratory at the Broad Institute of MIT/Harvard further showed promising potential along this line of research. This technology has identified a clear metabolic profiling of branch chain amino acids for risk of future pancreatic caner, proving its validity of metabolic profiling in cancer research. In addition, the methods have also passed our own rigorous reproducibility assessments. All these provide important ground work for the current proposal. The current study is using a targeted, LC-MS-based metabolite profiling platform to measure and compare metabolic profiles of prediagnostic blood samples collected from men subsequently diagnosed with PCa and sample of men who remained cancer-free in Physicians' Health Study (PHS). And test whether these relationships are independent of the known metabolic risk factors (overweight/obese, insulin marker C-peptide, insulin-like growth factor I (IGF-I), IGF binding protein 3, (IGFBP-3), and adiponectin) as well as the clinical characteristics defined as the D'Amico risk.

1. Keywords

Prostate cancer survivorship, metabolomic profiling, metabolic biomarkers

2. Accomplishments

What were the major goals of the project?

The three original aims were:

Aim 1: Explore and validate the metabolomic footprints for normal controls (n=50 x 2 cohorts) vs. three groups of cases (metastatic PCa at diagnosis, initially localized PCa and long-time survivors, and initially localized PCa but died of PCa; n=50 in each of the three groups, total n=150 cases x 2 cohorts);

Aim 2: Among men with initial localized PCa, explore and validate the metabolomic footprints for long-term survivors vs. men who subsequently died of PCa;

Aim 3: Test and validate whether these associations are independent of the known metabolic risk factors (overweight/obese, insulin marker C-peptide, insulin-like growth factor I (IGF-I), IGF binding protein 3 (IGFBP-3), and adiponectin), as well as the clinical characteristics defined as the clinical risk group.

In the original protocol, we plan to measure samples of PCa cases from both HPFS and PHS. However, the HPFS team has received separate grant for metabolomics measurement. Therefore, we amended our study population to focus only on the PHS. Due to the budget constraints, we cannot analyze a large number of blood samples for PCa cases. We, therefore, spend lots of time

during year one on discussing the sample selection strategy to select the most informative cases, controls and long-term survivors.

As a result, we modified specific aims as the following:

Aim 1: 1a. Compare to healthy men without cancer (at least at the time when the cases were diagnosed), metabolomic profiling for men with "high risk" (T1-3 and Gleason 8+) or metastasis at diagnosis; 1b. Among men with "high risk" (T1-3 and Gleason 8+) or metastasis at diagnosis, metabolomic profiling between men who died of the cancer vs. those who were still alive by 2012;

Aim 2: Compare the metabolomic profiles between men with "low-intermediate risk" (T1-3 and Gleason 2-7) PCa and died of the cancer with those who survived at least 10 years after diagnosis;

Aim 3: Test whether these associations are independent of the known metabolic risk factors (overweight/obese, insulin marker C-peptide, insulin-like growth factor I (IGF-I), IGF binding protein 3 (IGFBP-3), and adiponectin), as well as the clinical characteristics defined as the clinical risk.

What was accomplished under these goals?

Based on the available samples, we utilized matched case control design to select the blood samples to be measured. The selected blood samples are currently being pooling from our blood lab and we expect to have them ready to be sent to the MIT lab by the fall of 2014.

I. Sample selection

Based on the available samples, we utilized matched case control design to select the blood samples to be measured. The following part showed the matching method for each specific aim.

Aim 1: Study Population:

1) All population in the cohort;
2) Blood volume >100 ml;

Cases:

1) Incidence PCa cases 2) Localized and high grade cases or mets at diagnosis; 3) status in mortality file: died of PCa or alive;

Control Matching criteria:

1) Same age group at baseline: 40-<50 50-<60 6-<70 70+years
2) Same fasting >=8, 0<8 hrs
3) Controls have no cancer, or have cancer, but diagnosed after the last PCa diagnosis date in the age and fasting group.(we only have cancer information, no other disease info)
4) Frequency matching: get same percentile at each age group and total controls are 100.

Program: SAS proc surveyselect

Aim2: Study Population:

1) Incidence PCa cases with blood collected in 1982;

2) Localized and low grade cases;
3) Blood volume >100 ml;
Cases:
1) Status in mortality file: 1)PCa death; 2) Survived less than 10years
Control Matching criteria:
1) Same age at diagnosis
2) Same fasting >=8, 0<8 hrs
3) Same Gleason category: 2-6,7
4) Controls are alive now, and alive more than 10 years.
5) 1:1 match", program: proc sql and hash table

In summary, for aim 1, there are 109 cases who have localized ,high grade PCa (clinical stage T1-T3 , Gleason grade 8-10) and have 82 blood available 85 cases who have metastatic PCa (clinical stage T4N1M1 ,Gleason grade 2-10) and have 82 blood available cases must have 82 blood plasma volume >100, age at baseline and fasting status ,then total cases is 181. We matched 100 controls from participants in PHS exclude cases. Selected controls have 82 blood available (blood plasma volume >100ml), age at baseline and fasting status, cancer free or have cancer, but diagnosed after the same group of cases. For aim 2, 48 eligible cases were identified from PHS, those cases have localized low grade (clinical stage T1-T3, Gleason grade 2-7) PCa who died of PCa, survived less than 10 years and have 82 blood available (blood plasma volume >100). Among them, 43 got matched with controls, who have localized low grade (clinical stage T1-T3, Gleason grade 2-7) PCa, alive now and have been alive more than 10 years (Table 1).

Table 1: Final Result of sample selection

Classification (N)		Sample size	Matched controls
Aim 1 (All Population)			
Localized T1-T3 & Gleason 8-10	Died of PCa	43	
	Alive	57	
Metastatic PCa (T4N1M1)	Died of PCa	51	
	Alive	30	
	Total	**181**	
Healthy controls			**100**
Aim 2 (Incident PCa with 82 blood)			
Localized T1-T3 & Gleason 2-6 ,7	died of PCa	**48**	
	Long-term survivor 10 yr+ controls	487	**43**

Following this matching procedure, we selected a total of 372 (Aim1: 181 cases and 100 matched controls; Aim 2: 48 cases and 43 matched controls) blood samples for analyses. 28 QC samples were also included. After checking the blood lab staff, we have only successfully identify 329 out of 372 eligible samples, and 40 quality control samples from lab. We then decided to add 31 additional samples from PCa patients who have been died from other cancers. We sent a final number of 400 samples to Dr. Clish's lab at November, 2014.

II. Completed/ongoing studies & results

While waiting for the lab results, we have been working on analyzing the related metabolic biomarkers and writing up manuscripts on related topics.

a. Association of type 2 diabetes susceptibility variants with risk of advanced prostate cancer and progression to fatal outcome in the Breast and Prostate Cancer Cohort Consortium

A post-doctoral fellow at the Harvard School of Public Health, Mitchell Machiela, had used the Breast and Prostate Cancer Cohort Consortium (BPC3) study to conduct a genome-wide association study of 2,782 advanced PCa cases and 4,458 controls to evaluate whether 36 type 2 daibetes (T2D) susceptibility loci are associated with PCa risk and found ten T2D markers near 9 loci (NOTCH2, ADCY5, JAZF1, CDKN2A/B, TCF7L2, KCNQ1, MTNR1B, FTO, and HNF1B) were nominally associated with PCa ($P < 0.05$); the association for rs757210 at the HNF1B locus was significant when multiple comparisons were accounted for (adjusted $P = 0.001$). Genetic risk scores weighted by the T2D log odds ratio and multilocus kernel tests also indicated a significant relation between T2D variants and PCa risk. Paper is published by Am J Epidemiol.

To the best of our knowledge, these T2D risk variants have not been fully investigated for PCa progression to fatal outcome, especially using the genetic risk scores of T2D risk variants. Also, few studies have T2D phenotypes or sufficient power to assess whether T2D status (before or after PCa diagnosis) mediates the relationship between T2D risk variants and PCa risk. We therefore proposed to evaluate these T2D risk variants in association with PCa progression to fatal outcome. Changzheng Yuan is currently working on this project.

b.Insulin-like growth factor (IGF) pathway genetic polymorphisms, circulating IGF1 and IGFBP3 levels and prostate cancer survival

We conducted kernel machine pathway analysis to evaluate whether 530 tagging single-nucleotide polymorphism (SNP) in 26 IGF pathway-related genes were collectively associated with prostate cancer mortality among 5,887 prostate cancer patients (704 prostate cancer deaths) from 7 cohorts in the NCI Breast and Prostate Cancer Cohort Consortium (BPCa3).

IGF signaling pathway was associated with prostate cancer mortality (P=0.03), and SNP sets of *IGF2-AS* and *SSTR2* were the main contributors (both P=0.04) (Table 5). In SNP-specific analysis, 36 SNPs were associated with prostate cancer mortality with $P_{trend}<0.05$ but only 3 SNPs in the *IGF2-AS* remained significant after gene-based corrections. Two of the three SNPs were in perfect linkage disequilibrium ($r^2=1$ for rs1004446 and rs3741211) whereas the third rs4366464 was independent ($r^2=0.03$). The hazard ratios (HRs) per each additional risk allele were 1.19 (95% CI 1.06-1.34; $P_{trend}=0.003$) for rs3741211 and 1.44 (1.20-1.73; $P_{trend}=0.0001$) for rs4366464. Rs4366464 remained significant after correction for all the SNPs tested ($P_{trend.corr}=0.04$, $M_{eff}=424$). Pre-diagnostic circulating levels of IGF1 ($HR_{highest\ vs\ lowest\ quartile}$ 0.71; 95%CI 0.48-1.04) and IGFBP3 (HR 0.93; 95%CI 0.65-1.34) were not associated with prostate cancer mortality. The manuscript has been submitted to JNCI.

c. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development.

The pancreatic cancer group from Danna Farber Cancer Institute has also been working on the metabolomics of pancreatic cancer development. We are also working closely with this group on metabolomics data analysis.

This study utilized profiled metabolites in prediagnostic plasma from individuals with pancreatic cancer (cases) and matched controls from four prospective cohort studies. And find that elevated plasma levels of branched-chain amino acids (BCAAs) are associated with a greater than twofold increased risk of future pancreatic cancer diagnosis. This elevated risk was independent of known predisposing factors, with the strongest association observed among subjects with samples collected 2 to 5 years before diagnosis, when occult disease is probably present. We show that plasma BCAAs are also elevated in mice with early-stage pancreatic cancers driven by mutant *Kras* expression but not in mice with *Kras*-driven tumors in other tissues, and that breakdown of tissue protein accounts for the increase in plasma BCAAs that accompanies early-stage disease. Together, these findings suggest that increased whole-body protein breakdown is an early event in development of pancreatic ductal adenocarcinoma (PDAC). This manuscript was submitted to Nature Medicine.

d. Whole Milk Intake Is Associated with Prostate Cancer-Specific Mortality among U.S. Male Physicians

Previous studies have associated higher milk intake with greater prostate cancer (PCa) incidence, but little data are available concerning milk types and the relation between milk intake and risk of fatal PCa. We investigated the association between intake of dairy products and the incidence and survival of PCa during a 28-year follow-up in the Physicians' Health Study (n = 21,660) and a survival analysis among the incident PCa cases (n = 2806). Information on dairy product consumption was collected at baseline. PCa cases and deaths (n = 305) were confirmed during follow-up. Intake of total dairy products was associated with increased PCa incidence [HR: 1.12 (95% CI: 0.93, 1.35), ≥2.5 servings/d vs. <0.5 servings/d]. Skim/low-fat milk intake was positively associated with risk of low-grade, early stage, and screen-detected cancers, whereas whole milk intake was associated only with fatal PCa [HR: 1.49 (95% CI: 0.97, 2.28), ≥237 mL/d (1 serving/d) vs. rarely consumed]. In the survival analysis, whole milk intake remained associated with risk of progression to fatal disease after diagnosis [HR: 2.17 (95% CI: 1.34, 3.51)]. In this prospective cohort, higher intake of skim/low-fat milk was associated with a greater risk of non-aggressive PCa. Whole milk was consistently associated with a higher risk of fatal PCa and, among cases, higher risk of progression to death after diagnosis. These findings add further evidence to suggest the potential role of dairy products in the development and prognosis of PCa. The paper is published by J Nutr. We plan to link these findings with the metabolomics data once we get from the lab to further evaluate the underlie mechanisms.

e. Characterization of energy-related biomarkers measured before and after PCa diagnosis in predicting all-cause and PCa-specific mortality.

In the PHS, we defined "high energetic risk" as BMI>25 kg/m^2 and elevated C-peptide levels (in the highest quartile). We found that this "energetic risk" significantly predicted PCa mortality among men with localized disease at diagnosis independent of clinical characteristics. We replicated this association in an independent cohort, the Health Professionals Follow-up Study (HPFS).

In both cohorts, we found that incorporating this "energetic risk" to the D'Amico risk score (defined by three clinical perimeters: PSA, clinical stage, and Gleason score) significantly improved the predictability of PCa-specific mortality and all-cause mortality in men with initial diagnosis of localized cancer; the C-statistic for PCa-specific mortality was improved from 0.72 to 0.78 *(P<0.001*). Moreover, "energetic risk" identified ~20% of patients who are at high risk of disease specific mortality but are classified as low risk according to clinical characteristics. The resulting paper is undergoing peer-review. One major concern raised was the potential confounding by comorbidity and treatments. We therefore carefully evaluated the impact of these two factors from both cohorts and found little changes of the overall results.

f. Pre-diagnostic Obesity, Smoking and PCa survival

Although obesity and smoking has not been strongly associated with prostate cancer (PCa) incidence, merging evidence linked them to increased PCa-specific mortality.we investigated the associations of pre-diagnostic BMI and smoking status with risk of progression from time of PCa diagnosis to fatal outcome among 10,106 PCa patients from the NCI Breast and Prostate Cancer Cohort Consortium (BPC3). Changzheng Yuan is working on this project.

What opportunities for training and professional development has the project provided?

This provided has provided funding and research opportunities for several doctoral and post-doctoral students from Harvard T.H. Chan School of Public Health.

Machiela MJ and Yan Song are two former post-doctoral fellows working on this project and published two papers (see the publication list).

Yin Cao, graduated from the doctoral of science program from Epidemiology department, and a current post-doc student at Nutrition Department. One of her thesis paper was based on and supported by the current project.

Changzheng Yuan, doctoral candidate at Nutrition and Epidemiology Department. She is now working on three research topics related to this project, mainly focusing on obesity, T2DM and genetic variants related to prostate cancer development.

Meng Yang, postdoc fellow at Nutrition Department. She currently working on studying the BMI trajectory, dietary factors, metabolic biomarkers and prostate cancer survivorship.

CY and MY also work closely with the project leader and statisticians to discuss the study design and sample selections.

How were the results disseminated to communities of interest?

Nothing yet to report.

What do you plan to do during the next reporting period to accomplish the goals?

In year two, we plan to send the plasma samples to the MIT Broad Institute metabolomics lab for metabolomics assays. We will closely communicate with the lab director Dr. Clary Clish to ensure the assay quality control and control for batch variations. Once we have the data, we will conduct the analyses based on the proposed aims of metabolomic analysis and preparing for manuscripts.

3. Impact

What was the impact on the development of the principal discipline(s) of the project?
The most exiting findings from our group and MIT collaborators is the finding that elevated plasma levels of branched-chain amino acids (BCAAs) are associated with a greater than twofold increased risk of future pancreatic cancer diagnosis. This elevated risk was independent of known predisposing factors, with the strongest association observed among subjects with samples collected 2 to 5 years before diagnosis, when occult disease is probably present.

As for the proposed study, one notable strength is the use of unbiased metabolomic profiling to distinguish lethal from indolent disease, a major challenge in prostate cancer research. Since 80 to 90% of PCa cases diagnosed in the United States nowadays are confined to the prostate and two-thirds of the cases are localized or regional disease and low- to moderate- grade at diagnosis. Current use of clinical features cannot always reliably distinguish patients who will die from prostate cancer from those who do not. We hope that our study could help to identify novel metabolic biomarkers specifically associated with lethal outcome and to understand mechanisms leading to disease progression.

What was the impact on other disciplines?
Nothing yet to report.

What was the impact on technology transfer?
Nothing yet to report.

What was the impact on society beyond science and technology?
Nothing yet to report.

4. Changes/Problems

Changes in approach and reasons for change
As mentioned above, we now only focus on the PHS cohort.

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing yet to report.

Changes that had a significant impact on expenditures
Nothing yet to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing yet to report.

5. Products

Journal Publications:

1) Machiela MJ, Lindström S, Allen NE, et al**.** ***Association of type 2 diabetes susceptibility variants with advanced prostate cancer risk in the Breast and Prostate Cancer Cohort Consortium***. Am J Epidemiol. 2012 Dec 15;176(12):1121-9. PMID: 23193118

2) Song Y, Chavarro JE, Cao Y, et al. ***Whole Milk Intake Is Associated with Prostate Cancer-Specific Mortality among U.S. Male Physicians***. J Nutr. 2013 Feb;143(2): PMID:23256145

Other publications, conference papers, and presentations:

Yuan C, Cao Y, Chavarro J, Lindström S …, Ma J. *Prediagnostic body-mass index, smoking and prostate cancer survival in a multi-cohort consortium study.* A poster was presented at the Frontier of Cancer Prevention Research 2013 Conference in Washington DC, Nov. 2013.

6. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name	Jing Ma
Project Role:	PI
Researcher Identifier	
Nearest person month worked	
Contribution to Project	As the project PI, Dr. Ma has lead the weekly meetings for project team members. She direct and is responsible for the overall study design and performance, report and manuscript preparation
Funding Support	

Name	Jorge Chavarro
Project Role:	Co-Investigator
Researcher Identifier	
Nearest person month worked	
Contribution to Project	Dr. Chavarro works closely with Drs. Ma, Clish, and Qiu on data analysis, interpretation, and manuscript preparation
Funding Support	

Name	Weiliang Qiu
Project Role:	Biostatistician
Researcher Identifier	
Nearest person month worked	

Contribution to Project	As an experienced biostatistician based at the Channing Laboratory , Dr. Qiu takes the major responsibility of data mining and statistical analysis
Funding Support	

Name	Yin Cao
Project Role:	Post-doc fellow
Researcher Identifier	
Nearest person month worked	
Contribution to Project	Yin Cao mainly works on literature review on genetic factors and cancer development, data analysis and manuscript development.
Funding Support	

Name	Meng Yang
Project Role:	Post-doc fellow
Researcher Identifier	
Nearest person month worked	
Contribution to Project	Meng Yang mainly works on literature review on diet, metabolic biomarkers and cancer development, data analysis and manuscript development.
Funding Support	

Name	Changzheng Yuan
Project Role:	Graduate student
Researcher Identifier	
Nearest person month worked	
Contribution to Project	Changzheng Yuan mainly works on: 1)literature review on cancer related topics and methodology in study design/data analyses; 2) Data analysis of the Physician's Health Study based as well as other cohort-based research, such as BPC3 research; 3) Assist the PI and work closely with data manager/programmer on data analysis of clinical, demographic, questionnaire and biomarker; 4) Prepare data analyses report and develop research manuscript.
Funding Support	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report.

What other organizations were involved as partners?

Clary Clish, sub-contract PI, conducting metabolic analysis, the Metabolite Profiling Platform, Broad Institute of MIT/Harvard. Dr. Clish is an expert in metabolic profiling assay development and validations, and oversee the assay development, measurement, and data annotation at his laboratory.

7. Special Reporting Requirements

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to https://ers.amedd.army.mil for each unique award.
QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

No.

8. Appendices

1. Machiela MJ, Lindström S, Allen NE, Haiman CA, Albanes D, Barricarte A, Berndt SI, Bueno-de-Mesquita HB, Chanock S, Gaziano JM, Gapstur SM, Giovannucci E, Henderson BE, Jacobs EJ, Kolonel LN, Krogh V, **Ma J**, Stampfer MJ, Stevens VL, Stram DO, Tjønneland A, Travis R, Willett WC, Hunter DJ, Le Marchand L, Kraft P. Association of type 2 diabetes susceptibility variants with advanced prostate cancer risk in the Breast and Prostate Cancer Cohort Consortium. Am J Epidemiol. 2012 Dec 15;176(12):1121-9. PMID: 23193118
2. Song Y, Chavarro JE, Cao Y, Qiu W, Mucci L, Sesso HD, Stampfer MJ, Giovannucci E, Pollak M, Liu S, **Ma J.** Whole Milk Intake Is Associated with Prostate Cancer-Specific Mortality among U.S. Male Physicians.J Nutr. 2013 Feb;143(2): PMID:23256145